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Myeloablative Cord Blood Transplantation in Adults with Acute Leukemia: Comparison of Two Different Transplant Platforms

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A B S T R A C T

We compared the clinical outcomes of adults with acute leukemia that received single-unit umbilical cord blood transplantation (sUCBT) after conditioning with a busulfan/antithymocyte globulin (BU-ATG)–based regimen at University Hospital La Fe (n = 102) or double-unit UCBT (dUCBT) after conditioning with a total body irradiation (TBI)–based regimen at the University of Minnesota (n = 91). Nonrelapse mortality, relapse and disease-free survival were similar in the 2 groups. Multivariate analyses, showed more rapid neutrophil (hazard ratio [HR], .6; 95% confidence interval [CI], .45 to .80; $P = .0006$) and platelet recovery (HR, .59; 95% CI, .43 to.83; $P = .002$) after the BU-ATG-based conditioning and sUCBT. Although there was a lower risk of acute graft-versus-host disease (GVHD) grade II to IV (HR, 2.81; 95% CI, 1.75 to 4.35; $P < .001$) after BU-ATG and sUCBT, the incidences of grade III to IV acute and chronic GVHD were similar between the 2 groups. Regarding disease-specific outcomes, disease-free survival in both acute myeloid leukemia and acute lymphoblastic leukemia (ALL) patients were not significantly different; however, a significantly lower relapse rate was found in patients with ALL treated with TBI and dUCBT (HR, .3; 95% CI, .12 to .84; $P = .02$). In the context of these specific treatment platforms, our study demonstrates that sUCB and dUCBT offer similar outcomes.

INTRODUCTION

Umbilical cord blood (UCB) has become a frequently used source of hematopoietic progenitor cells for allogeneic transplantation in patients with acute leukemia [1-4]. Early studies in adults reported low rates of engraftment, which were mainly attributed to the low progenitor cell content of UCB grafts [5-7]. For this reason, most centers have adopted a minimum cell dose threshold of 2.5×10^7 nucleated cells per kilogram actual body weight. Unfortunately such a threshold would exclude many adults from UCB transplantation (UCBT). As a result, the double UCB transplantation (dUCBT) strategy was established to overcome this limitation and make UCB an adequate source of hematopoietic stem cells for nearly all adults [8], and many adults receive a dUCBT if an adequate single unit is not available [9].

Recent improvements in treatment regimens and UCB unit selection algorithms have led some centers to re-evaluate the cell dose limit. In fact, previous reports have shown that high rates of engraftment can be achieved with lower cell dose contents using an optimized busulfan-antithymocyte globulin (BU-ATG)–based regimen conditioning regimen and cord blood unit selection, making single-unit UCBT (sUCBT) widely available [10]. If the cell dose limit could be reduced, the added cost of the second unit might be avoided.

The aim of this study was to compare the clinical outcomes of adults with acute leukemia undergoing UCBT at 2 institutions using different transplantation platforms regarding conditioning regimen, UCB unit selection, and graft-versus-host disease (GVHD) prophylaxis.

PATIENTS AND METHODS

Eligibility Criteria

All consecutive adult patients over 15 years of age with acute leukemia undergoing first stem cell transplantation with UCB from an unrelated donor using myeloablative conditioning regimen between January 2001 and December 2009 were eligible. All patients at University Hospital La Fe (Valencia) underwent transplantation with a single unit. Although about 25% of adults at the University of Minnesota (Minneapolis) receive a single unit containing $>2.5 \times 10^7$ nucleated cells/kg, only recipients of a dUCBT were included in the study. The upper age limit for myeloablative UCBT was 45 and 55 years in Minneapolis and Valencia, respectively. Each center's institutional review boards approved treatment protocols and informed consent was obtained according to the principles of the Declaration of Helsinki.

The treatment plans, including of unit selection, conditioning regimen, immune suppression, and supportive care, have been reported by University Hospital La Fe [1-4,11] and University of Minnesota groups [5-8,12] and are summarized below.

Umbilical Cord Blood Unit Selection

Graft selection algorithm required that UCB units to be ≥4/6 HLA matched with the recipient (HLA class I antigens [A and B] considering the antigen level and class II antigen [DRB1] considering allele level resolution DNA typing).

University Hospital La Fe

A total nucleated cell dose (TNC) $\geq 1.5 \times 10^7$/kg recipient's body weight was required until 2005. From 2006, TNC $\geq 2 \times 10^7$/kg and CD34+ cell dose $\geq 1 \times 10^5$/kg recipient's body weight were required. Cell dose was considered the most important criteria for unit selection. All patients for which donor search was initiated had a suitable UCB unit available according to the above-mentioned criteria.

University of Minnesota

All patients from the University of Minnesota included in this analysis received dUCB grafts selected according to the institutional algorithm. The

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combined minimum TNC dose was $\geq 2.5 \times 10^7$/kg of recipient's body weight with 1 unit having a cell dose $\geq 1.5 \times 10^7$/kg. The 2 UCB units were infused in random order within 30 minutes of each other.

Conditioning Regimen and GVHD Prophylaxis

University Hospital La Fe

All patients received thiotepa, busulfan, cyclophospamide or fludarabine, and ATG [4-8]. Until March 2005, 30 patients received thiotepa (10 mg/kg), busulfan (9.6 mg/kg i.v.), cyclophosphamide (120 mg/kg) and ATG (Thymoglobulin, Genzyme Transplant, Cambridge, MA; 8 mg/kg). From March 2005, the remaining 72 patients received the same preparative regimen but replacing cyclophosphamide by fludarabine (150 mg/m^2).

For GVHD prophylaxis, all patients received cyclosporine combined with either long course prednisone in the first 62 patients (.5 mg/kg/day on days +7 to +14, 1 mg/kg/day on days +14 to +28, with slow tapering until discontinuation on day +180), mycophenlate mofetil (MMF) (15 mg/kg/12 hours until day +28) in the following 35 patients, or a short course of prednisone in the last 5 patients (1 mg/kg/day on days +14 to +28).

University of Minnesota

All patients received myeloablative conditioning consisting of cyclophosphamide 120 mg/kg i.v. divided in 2 daily doses, fludarabine 75 mg/m^2 i.v. divided in 3 daily doses, and total body irradiation (1320 cGy) delivered in 8 fractions over 4 days. The GVHD prophylaxis with cyclosporine A, starting intravenously on day -3 with a target trough level of 200 μg/L to 400 μg/L, that, in case of no GVHD, was tapered over 10 weeks starting at day +100. Patients also received MMF starting i.v. at day −3, before 2006 at a dose of 2 g/day and, from 2006, 3 g/day, that was discontinued at day +30 in case of no acute GVHD [8,9].

Definitions

Myeloid recovery was defined as the first day of an absolute neutrophil count of 0.5×10^9/L lasting for 3 or more consecutive days. Platelet recovery was defined as the first day of a platelet count of 20×10^9/L or higher, without transfusion support for 7 consecutive days. Patients who survived more than 28 days after transplantation and who failed to achieve myeloid engraftment were considered as primary graft failure. Acute and chronic GVHD were defined and graded according to standard criteria [10,13-15]. Disease stage at the time of transplantation was classified as follows: (1) early stage: first complete remission (CR1); (2) intermediate stage: second or further CR; and (3) advanced stage: not in remission. Donor and recipient HLA match for dUCBT was considered taking into account the cord blood unit with the highest HLA disparity. Nonrelapse mortality (NRM) was defined as death from any cause without evidence of relapse. Leukemia-free survival (LFS) was defined as survival from the time of transplantation without evidence of leukemia relapse.

Statistical Analysis

Patient and transplantation characteristics from different series were compared using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The probabilities of engraftment, NRM, GVHD, and relapse were estimated by the cumulative incidence method (marginal probability) [16-17]. For cumulative incidence analyses of engraftment, GVHD, and relapse, death in CR was considered as a competing cause of failure, whereas relapse was the competing event for NRM. Unadjusted time-to-event analyses were performed using the Kaplan-Meier estimate [18], and, for comparisons, the log-rank tests [19]. Disease-free survival was calculated from the date of UCBT. In the analysis of LFS, relapse, or death in CR, whichever occurred first was considered an uncensored event. The follow-up of the patients was updated on October 1, 2012. A Cox proportional hazards model [20] or the Fine and Gray method for competing events [21] were used for multivariable analysis. Variables included in the models were treatment platform, age, gender, recipient body weight, transplantation period, recipient cytomegalovirus serostatus, diagnosis (acute myeloid leukemia [AML] versus acute lymphoblastic leukemia [ALL]), disease stage at transplantation, and HLA compatibility. Statistical analysis were conducted using R version 2.12.2 (The CRAN project) with packages, survival v2.36-10, Design 2.3-0, prodlim v1.2.1 and cmprsk v2.2-2 [22].

RESULTS

Patient, Umbilical Cord Blood Unit, and Transplantation Characteristics

Table 1 summarizes the demographic characteristics of the 102 and 91 patients at the University Hospital La Fe and the University of Minnesota, respectively. Patient and disease characteristics were similar in both groups, except for a higher proportion of patients that were CMV seropositive (77% versus 54%; $P = .0009$), and with relapsed or refractory disease at time of transplantation (27% versus 8%; $P = .003$) in the Valencia group. The median follow-up for surviving patients was 76 months (range, 39 to 130) and 61 months (range, 23 to 121), respectively. The median date of transplantation was December 2006 in the Valencia cohort and June 2006 in the Minneapolis group. Table 2 summarizes the characteristics of the cord blood units.

Table 1
Characteristics of Patients

Characteristic	Valencia Cohort	Minneapolis Cohort	*P* Value
Patients, n	102	91	
Age, median (range), yr	30 (16 to 52)	28 (15 to 45)	.13
Male sex, n (%)	65 (64)	49 (54)	.21
Weight, median (range), kg	70 (37 to 112)	73 (43 to 149)	.4
Diagnosis, n (%)			.42
AML	49 (48)	50 (55)	
ALL	53 (52)	41 (45)	
Disease stage at transplantation, n (%)			.0003
First complete remission	54 (53)	49 (54)	
Second or beyond complete remission	20 (20)	35 (38)	
Relapsed or refractory	28 (27)	7 (8)	
CMV seropositive recipient, n (%)	79 (77)	49 (54)	.0009
Time from diagnosis to transplantation for patients in CR1, median (range), mo	182 (27 to 331)	127 (67 to 343)	.4

CMV indicates cytomegalovirus; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia.
Percentages may not total 100 because of rounding.

Hematopoietic Engraftment

Myeloid engraftment

In the Valencia cohort, 2 patients died on days 12 and 19 after UCB infusion without evidence of myeloid engraftment, 3 patients experienced primary graft failure, 2 patients with initial neutrophil recovery subsequently lost the graft, and the remaining 95 patients achieved stable myeloid engraftment at a median time of 20 days (range, 12 to 57). In the Minneapolis cohort, 12 patients experienced primary graft failure, 1 patient with initial neutrophil recovery

Table 2
Graft and Transplantation-Related Characteristics

Characteristic	Valencia Platform	Minneapolis Platform	*P* Value
HLA compatibility, n (%)*			.24
6 of 6	7 (7)	6 (7)	
5 of 6	21 (21)	28 (31)	
4 of 6	74 (73)	57 (63)	
ABO blood group mismatch, n (%)			<.0001
Major	24 (24)	43 (47)	
Minor	34 (33)	35 (38)	
None	44 (43)	13 (14)	
Nucleated cells infused $\times 10^7$/kg, median, n (range)	2.5 (1 to 5.8)	3.6 (2 to 6.3)†	<.0001

Percentages may not sum to 100 because of rounding.
* For double umbilical cord transplantation, the unit with the highest HLA disparity was considered.
† After adding the cell dose of 2 cord blood units infused

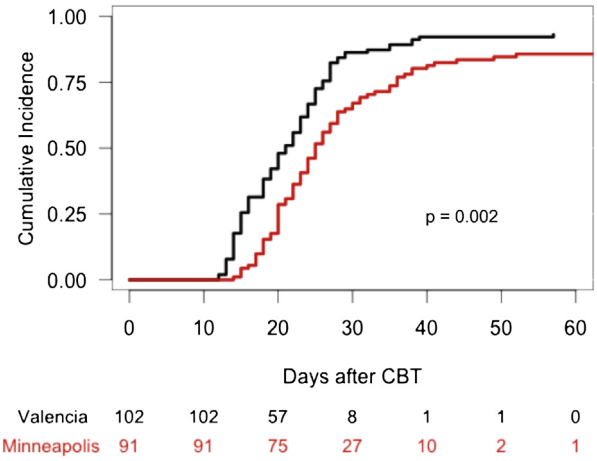

Figure 1. Cumulative incidence of neutrophil recovery after UCB transplantation with either Valencia or Minneapolis platforms.

subsequently lost the graft, and the remaining 78 patients achieved stable myeloid recovery at a median time of 24 days (range, 14 to 52). The cumulative incidence of sustained myeloid recovery at 60 days in the Valencia and Minneapolis cohorts was 93% and 86%, respectively ($P = .002$) (Figure 1). In multivariable analysis, the Valencia platform was associated with a better neutrophil recovery ($P = .0006$) (Table 3).

Time to neutrophil recovery and engraftment correlated with CD34+ cell dose in the Valencia (HR, 1.19; 95% CI, 1.06 to 1.34; $P = .003$) and in the Minneapolis (HR, 1.15; 95% CI, 1.07 to 1.24; $P = .0003$) cohorts.

Platelet engraftment

Of the 95 patients with myeloid engraftment in the Valencia cohort, 16 patients died between 22 and 250 days after transplantation without platelet recovery. The remaining 79 patients had platelet engraftment at a median time of 53 days (range, 23 to 142). Of the 78 patients with myeloid engraftment in the Minneapolis cohort, 17 patients died between 44 and 143 days after transplantation without platelet recovery. The remaining 61 patients had platelet engraftment at a median time of 97 days (range, 35 to 450). The cumulative incidence of sustained platelet engraftment at 100 days in the Valencia and Minneapolis cohorts was 77% and 62%, respectively ($P = .001$). In multivariable analysis, the Valencia platform was associated with a better platelet recovery ($P = .002$) (Table 3).

Table 3
Multivariable Analysis of Short and Long-Term Outcomes for All Patients according to UCBT Platform

Outcome	Relative Risk (95% CI)		*P* Value
	Valencia Platform	Minneapolis Platform	
Myeloid engraftment	1	.6 (.44 to .802)	.0006
Platelet engraftment	1	.59 (.43 to .83)	.002
Acute GVHD, grade II to IV	1	2.81 (1.75 to 4.35)	<.0001
Chronic GVHD	1	.7 (.31 to 1.60)	.4
Transplantation-related mortality	1	1.06 (.66 to 1.71)	.8
Relapse	1	.52 (.25 to 1.08)	.08
Leukemia-free survival	1	1.27 (.86 to 1.88)	.23

GVHD indicates graft-versus-host disease.

GVHD

Acute GVHD

In the Valencia cohort, 51 of the 95 evaluable patients with stable engraftment developed acute GVHD (aGVHD). Acute GVHD grade I was observed in 25 patients, grade II in 10 patients, grade III in 12 patients, and grade IV in 4 patients. The median time to the development of acute GVHD grade II to IV was 16 days (range, 8 to 91). In the Minneapolis cohort, 59 of the 78 evaluable patients with stable engraftment developed aGVHD. Acute GVHD grade I was observed in 5 patients, grade II in 34 patients, grade III in 16 patients, and grade IV in 4 patients. The median time to the development of acute GVHD grade II to IV was 23 days (range, 13 to 69).

The cumulative incidence of aGVHD at 100 days in the Valencia and Minneapolis cohorts was 28% and 69% for grade II to IV, respectively ($P < .0001$), whereas for grade III to IV it was 17% and 26%, respectively ($P = .2$). In multivariable analysis, the Minneapolis platform was associated with an increased risk of aGVHD grades II to IV ($P < .0001$) (Table 3). No factor was associated with the risk of grade III to IV aGVHD.

Chronic GVHD

Thirty-nine of 78 patients at risk in the Valencia cohort developed chronic GVHD (cGVHD) at a median time of 140 days (range, 70 to 415). Chronic GVHD was limited in 16 patients and extensive in 23 patients. In the Minneapolis cohort, 24 of 67 patients at risk developed cGVHD at a median time of 153 days (range, 92 to 558). Chronic GVHD was limited in 5 patients and extensive in the remaining 19 patients.

The 2-year cumulative incidence of any cGVHD and extensive cGVHD in the Valencia and Minneapolis cohorts was 50% and 36% ($P = .06$) and 29% and 28% ($P = .8$), respectively. No factor was associated with the risk of cGVHD in multivariable analysis.

NRM

Thirty-six patients in the Valencia cohort died without prior relapse at a median time of 125 days after transplantation (range, 12 to 2535), whereas in the Minneapolis cohort, 32 patients died at a median time of 62 days after transplantation (range, 24 to 765). The cumulative incidence of NRM was similar in both groups ($P = .8$). For patients in the Valencia cohort, the incidence of NRM at 100 days, 180 days, and 5 years was 13%, 20%, and 34%, respectively. For patients in the Minneapolis cohort, the incidence of NRM at 100 days, 180 days, and 5 years was 24%, 30%, and 35%, respectively. No factor was associated with the risk of NRM in multivariable analysis.

Relapse

Overall, 32 patients in the Valencia cohort relapsed at a median time of 4.5 months (range, 1 to 50) and 12 patients in the Minneapolis cohort relapsed at a median time of 6.8 months (range, 1 to 22). All relapsed patients died at a median time of 64 days (range, 2 to 1129). Relapse incidence was different depending on diagnosis, with a 5-year cumulative incidence of relapse of 40% and 24% for patients with ALL and AML, respectively ($P = .04$). The 5-year cumulative incidence of relapse was 42% for the Valencia cohort and 19% for the Minneapolis cohort ($P = .004$). The 5-year cumulative incidence of relapse was 70% versus 66% ($P = .9$) for patients in advanced stage and 31% versus 14% ($P = .04$) for patients in CR

for the Valencia and Minneapolis cohorts, respectively. However, in multivariable analysis, only advanced disease status at time of transplantation was associated with increased risk of relapse ($P < .0001$).

When the analysis was restricted to patients with AML, the 5-year cumulative incidence of relapse was 23% and 13% for the Valencia and Minneapolis cohorts, respectively ($P = .3$). In multivariable analysis, advanced disease status at time of transplantation ($P < .0001$) and better HLA match (6/6 versus 5/6 versus 4/6) ($P < .001$) were the only independent factors independently associated with an increased risk of relapse (Table 4).

In patients with ALL, the 5-year cumulative incidence of relapse was 40% and 12% for the Valencia and Minneapolis cohorts, respectively ($P = .003$). In multivariable analysis, advanced disease status at time of transplantation ($P = .0006$) and the Valencia platform ($P = .02$) were associated with an increased risk of relapse (Table 4).

LFS

Thirty-four patients in the Valencia cohort and 47 patients in the Minneapolis cohort were alive and leukemia free after UCB transplantation at last follow-up. The overall LFS at 5 years was 34% and 52% for the Valencia and Minneapolis cohorts, respectively ($P = .05$). The 5-year LFS was 21% versus 29% ($P = .9$) for patients in advanced stage, and 40% versus 53% ($P = .2$) for patients in CR for the Valencia and Minneapolis cohorts, respectively. The 5-year LFS was 49% for patients with AML and 35% for patients with ALL ($P = .04$). In multivariable analysis, advanced disease status at time of transplantation was the only factor associated with higher risk of treatment failure ($P < .0001$).

The 5-year LFS for patients with AML was 45% for patients in the Valencia cohort and 54% in the Minneapolis cohort ($P = .4$) and 50% versus 55% ($P = .7$) for patients in CR, respectively (Figure 2). No factor was significantly associated with LFS in patients with AML in multivariable analysis. In patients with ALL, the 5-year LFS was 24% for patients in the Valencia cohort and 49% for those in the Minneapolis cohort ($P = .08$), and 30% versus 51% ($P = .2$) for patients in CR, respectively (Figure 3). In multivariable analysis, advanced disease status at time of transplantation was the only factor associated with higher risk of treatment failure ($P = .007$) (Table 4).

DISCUSSION

This study shows the relative efficacy of 2 UCBT platforms in adults with acute leukemia, which were carried out at 2 institutions using either a BU-ATG–based conditioning with sUCBT (Valencia platform) and TBI-based conditioning with dUCBT (Minneapolis platform). The main observation of this study is that sUCBT can be a suitable graft source. Although numerous reports have previously established the minimum cell dose threshold of 2.5×10^7 nucleated cells/kg, it is possible that this needs to be reconsidered, especially in the context of specific conditioning regimens. Whether the same results would have been observed with a sUCB unit after cyclophosphamide, fludarabine, and TBI as used in Minneapolis is not known. This might be addressed in future studies.

In the present study, we have had the opportunity to compare the outcome of 2 relatively large single-center series of adult patients with acute leukemia undergoing UCBT in 2 institutions experienced in UCBT. High rates of myeloid and platelet engraftment were achieved in the Valencia cohort and compare favorably with the Minneapolis cohort and with those reported in registry-based studies [23,24]. The addition of thiotepa to a BU-ATG–based conditioning regimen, as used in the Valencia cohort, appears to permit the routine use of lower dosed single units. Furthermore, it is possible that MMF may delay or reduce engraftment in some patients, as myelosuppression is a known complication and has been previously reported [25-27]. Why a faster engraftment and a lower graft failure rate in the Valencia cohort did not translate into a lower NRM remains unexplained and is probably multifactorial.

As previously described [28], grade II acute GVHD with involvement principally of the skin was more frequently observed in recipients of dUCBT as compared with recipients of UCBT, without a clear impact on NRM. The reason for the relatively low GVHD rate in the Valencia cohort is unproven, but we speculate that the use of rabbit ATG in the conditioning regimen may have contributed to this observation. Although it is possible that a lower CD3 cell dose inherent in

Table 4
Multivariable Analysis of Disease-Specific Outcomes: Relapse Risk and Leukemia-Free Survival

Outcome	Variable	Acute Myeloid Leukemia		Acute Lymphoblastic Leukemia	
		Relative risk (95% CI)	*P* Value	Relative Risk (95% CI)	*P* Value
Relapse					
	UCBT platform		.3		.02
	Valencia	1		1	
	Minneapolis	.6 (.24 to 1.57)		.3 (.12 to .84)	
	Disease status		<.0001		.0006
	Complete remission	1		1	
	Relapse/refractory	10.1 (3.50 to 29.1)		4.32 (1.86 to 9.74)	
	HLA match				
	6/6	1			
	5/6	.12 (.02 to .60)	.01	-	
	4/6	.09 (.03 to .31)	<.0001	-	
Leukemia-free survival					
	UCBT platform		.4		.15
	Valencia	1		1	
	Minneapolis	1.26 (.73 to 2.19)		1.48 (.87 to 2.54)	
	Disease status				.007
	Complete remission	-		1	
	Relapse/refractory	-		.44 (.24 to .80)	

UCBT indicates umbilical cord blood transplantation.

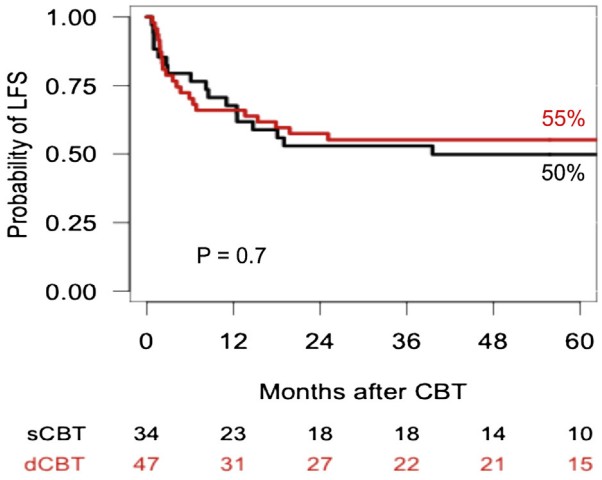

Figure 2. Probability of leukemia-free survival in patients with acute myeloid leukemia in remission after UCB transplantation with either Valencia or Minneapolis platforms.

the use of a single unit may have a played a role, prior studies have not observed an association between CD3 cell dose and acute GVHD. Incidences of acute grade III to IV and chronic GVHD were comparable in both cohorts. Although the addition of ATG could have hampered immune reconstitution in the Valencia cohort, a detailed analysis is unavailable. However, there was no significant difference in NRM in the present study and the incidence of cytomegalovirus reactivation previously reported from both groups was also similar [29,30].

Regarding relapse, it has been suggested a lower rate of relapse for patients receiving dUCBT indicates a potentially higher graft-versus-leukemia (GVL) effect [12,31,32]. However, this is, to date, an unexplained finding that has not been uniformly confirmed [33]. In the present study, the only variable with independent prognostic value for relapse was disease stage at time of transplantation, and after adjusting for this variable and various known risk factors, relapse was not associated with the cohort. Interestingly, relapse risk may be more associated with degree of HLA mismatch rather

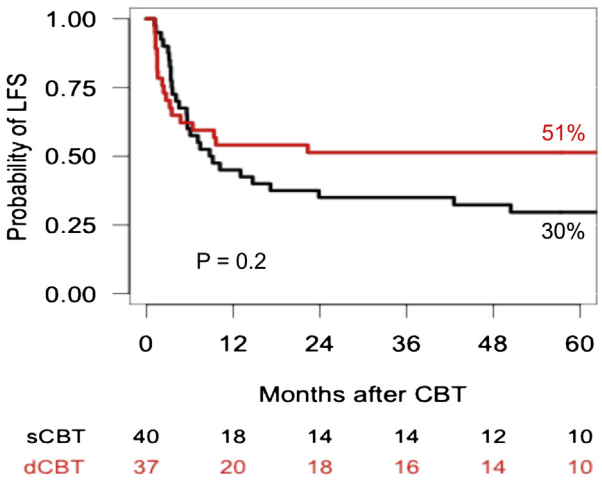

Figure 3. Probability of leukemia-free survival in patients with acute lymphoblastic leukemia in remission after UCB transplantation with either Valencia or Minneapolis platforms.

than the use of a dUCBT, as has been previously suggested by other studies [12]. In fact, for both groups, we observed an impressive reduction in the risk of relapse in patients with AML, suggesting an enhanced GVL effect for patients who underwent transplantation with UCB units with a higher HLA disparity. In this regard, previous registry-based studies from Eurocord [34] and the Japanese Society for Hematopoietic Cell Transplantation group [35] have also found that UCBTs with a higher HLA disparity had a lower probability of relapse. In contrast to pediatric patients, this effect does not seem to be counterbalanced with an increased NRM as suggested by large registry-based studies [35-37]. Although there was a lower risk of relapse in the Minneapolis patients with ALL, it is unclear whether this was due to the conditioning that included TBI, the use of 2 units, or the absence of in vivo T cell depletion with ATG.

In conclusion, this retrospective study demonstrated that in the context of the specific treatment platforms employed in Valencia and Minneapolis, sUCB and dUCBT offer similar outcomes. Future studies are needed to determine whether this finding is true for all or only specific scenarios. In addition, the finding that HLA mismatch does not compromise LFS and may indeed enhance the GVL effect also needs further investigation. Together, these 2 findings could have a significant impact on the practice of transplant medicine.

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